IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,258,062 :
Issued: March 24, 1981 :
Inventors: Rochus JONAS et al. :
For: PHENOXY-AMINO-PROPANOLS :

Box: Pat. Ext.

#12

TRANSMITTAL LETTER

Honorable ~~Commissioner~~ of
~~Patents and Trademarks~~
BOX PATENT EXTENSION
Washington, D.C. 20231

~~Sir:~~

Being filed herewith are the following papers:

1. Application for Extension of Patent Term Under 35 U.S.C. §156;
2. Declaration Under 37 C.F.R. §1.740(b);
3. Attachment A (copy of U.S. Patent No. 4,258,062);
4. Attachment B (brief description under 37 C.F.R. §1.755); and
5. A certified duplicate of all of the above.

Authorization is hereby granted to charge the fee of $1000 under 37 C.F.R. §1.20(j) for filing of an application for extension of the term of a patent to counsel's Deposit Account No. 13-3402. Two copies of this page are attached for this purpose. Authorization is also granted to charge any other fee which might be necessary in conjunction with this filing.

Respectfully submitted,

P 30049 10/16/92 4258062

13-3402 03 41 1,000.00CH

Harry B. Shubin
Reg. No. 32,004

MILLEN, WHITE & ZELANO, P.C.
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Filed: September 28, 1992
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 4,258,062	Box: Pat. Ext.
Issued:	March 24, 1981	
Inventors:	Rochus Jonas Karl-Heinz Becker Hans-Joachim Enenkel Klaus Minck Hans-Jochen Schliep	
For:	PHENOXY-AMINO-PROPANOLS	

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

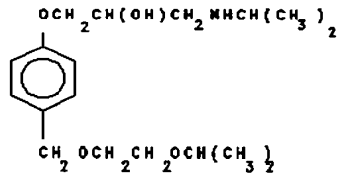
Honorable Commissioner of
Patents and Trademarks
BOX PATENT EXTENSION
Washington, D.C. 20231

Sir:

Applicant, E. Merck GmbH, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,258,062, granted to Rochus Jonas, Karl-Heinz Becker, Hans-Joachim Enenkel, Klaus Minck, Hans-Jochen Schliep, on March 24, 1981 November 2, 1982, for "PHENOXY-AMINO-PROPANOLS".

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. §1.710-§1.785). For the convenience of the U.S. Patent and Trademark Office, the information presented in this application is in a format which follows the requirements of 37 C.F.R. §1.740.

1. ZEBETA® contains, as the active ingredient, BISOPROLOL FUMARATE, whose chemical name is 1-(p-2-isopropoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol fumarate, which is a fumarate salt of a compound having the following structural formula:



2. The approved product, ZEBETA®, was subject to regulatory review under the Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

3. The approved product, ZEBETA®, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on July 31, 1992.

4. The only active ingredient in ZEBETA® is bisoprolol fumarate, which has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 19-982 of the Food and Drug Administration (FDA).

5. This application for extension of patent term under 35 U.S.C. §156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. §1.720(f), which period will expire September 29, 1992.

6. The complete identification of the patent for which extension is being sought is as follows:

Inventors:	Rochus Jonas Karl-Heinz Becker Hans-Joachim Enenkel Klaus Minck Hans-Jochen Schliep
Patent No.:	4,258,062
Issue Date:	March 24, 1981
Expiration Date:	March 24, 1998

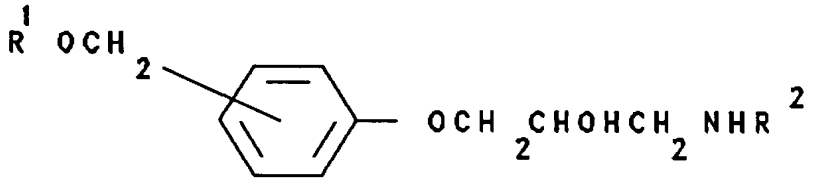
7. See Attachment A for a complete copy of the patent identified in paragraph 6 hereof.

8. No disclaimer, certificate of correction, or reexamination certificate has been issued with regard to U.S.

Patent No. 4,258,062. Maintenance fees for the patent are not required, as the patent was filed before December 12, 1980. Therefore, no receipt of maintenance fee payment has been issued.

9. U.S. Patent No. 4,258,062 claims the approved product. Specifically, the active ingredient bisoprolol fumarate is claimed in claim 1, which follows:

1. Phenoxy-amino-propanols of the formula



wherein R^1 is p-alkoxyalkyl with 2-6 atoms; and R^2 is alkyl or hydroxyalkyl with 1-6 atoms in each case, cycloalkyl with 3-8 C atoms or aralkyl or aralkyl wherein the aryl radical is mono- to tri-substituted by alkyl, alkoxy, OH, F, Cl or combinations thereof, with a total of 7-15 C atoms in each case, and the physiologically acceptable acid addition salts thereof.

(It is noted that claim 9 recites bisoprolol per se, but does not claim the salt; therefore, the claim does not literally encompass the approved product. Claim 9 would read on the approved product under the Doctrine of Equivalents.)

10. The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory period are as follows: The first Investigational New Drug Application (IND 24-773) for bisoprolol (for the indication of hypertension) was filed August 17, 1984. (A second IND, No. 26-072, was filed March 15, 1985, for the indication of angina. No NDA for angina was filed. The New Drug Application (NDA-19-982) for ZEBETA® (bisoprolol fumarate, for hypertension) was submitted to and approved by the FDA on July 28, 1989, and July 31, 1992, respectively.

11. A brief description of the activities undertaken by assignee's clinical research organization (CRO), Quincy Research Management Services, and later by assignee's licensee, Lederle Laboratories, during the applicable regulatory review period is attached as "Attachment B" and is a chronological synopsis of the major communications between assignee's CRO or licensee and the FDA from August 17, 1984, to July 31, 1992.

12. Applicant is of the opinion that U.S. Patent No. 4,357,324 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. §156(a); 37 C.F.R. §1.720(a)
U.S. Patent No. 4,258,062 claims a product.

b. 35 U.S.C. §156(a)(1); 37 C.F.R. §1.720(g)
The term of U.S. Patent No. 4,258,062 has not expired before submission of this application.

c. 35 U.S.C. §156(a)(2); 37 C.F.R. §1.720(b)
The term of U.S. Patent No. 4,258,062 has never been extended.

d. 35 U.S.C. §156(a)(3); 37 C.F.R. §1.730
The application for extension is submitted by the authorized agent or the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. §156(a)(4); 37 C.F.R. §1.720(d)
The product ZEBETA® has been subjected to a regulatory review period, as defined in 35 U.S.C. §156(g), before its commercial marketing or use.

f. 35 U.S.C. §156(a)(5)(A); 37 C.F.R. §1.720(e)(1)
The commercial marketing or use of the product ZEBETA® after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetics Act (21 U.S.C. §355), under which such regulatory review period occurred.

g. 35 U.S.C. §156(c)(4); 37 C.F.R. §1.720(h)

No other patent has been extended for the same regulatory review period for the product ZEBETA®.

h. 35 U.S.C. §156(d)(1); 37 C.F.R. §1.720(f)
The application is submitted within the permitted 60-day period, said period beginning on the date the product first received permission for commercial marketing or use.

i. The length of extension of the patent term of U.S. Patent No. 4,258,062 claimed by applicant is two years. The length of extension was determined pursuant to 37 C.F.R. §1.775 as follows:

(i). The regulatory review period under 35 U.S.C. §156(g)(1)(B) began February 4, 1983, and ended July 31, 1992, which is a total of 2875 days, which is the sum of ii and iii below:

(ii). The period of review under 35 U.S.C. §156(g)(1)(B)(i), the "Testing Period", began on September 16, 1984 (since the IND was filed 30 days prior to test date and was not disapproved by the FDA during that period), and ended on July 28, 1989, which is 1776 days.

iii. The period of review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period", began on July 28, 1989, and ended July 31, 1992, which is 1099 days.

j. The regulatory review period upon which the period of extension is calculated is the entire regulatory review period, as determined in subparagraph 12(i)(i) (2875 days) less

(i) the number of days in the regulatory review period which were on or before the date on which the patent issued, March 24, 1981, which is zero (0) days; and

(ii) the number of days during which applicant did not act with due diligence, which is zero (0) days; and

(iii) one-half the number of days determined in subparagraph 12(i)(ii) after subtracting therefrom the number of days of subparagraphs 12(j)(i) and (j)(ii) (zero in total) or 888 days.

This total is now 1987 days.

k. The number of days as determined in subparagraph 12(j)(iii) (1987 days) when added to the original term of the patent would result in the date September 1, 2003.

l. Fourteen (14) years, when added to the date of NDA approval (July 31, 1992), would result in the date July 31, 2006.

m. The earliest date as determined in paragraphs 12k and 12l is September 1, 2003.

n. Both the issuance of the original patent and the submission of the request for exemption occurred before September 24, 1984; and the commercial marketing or use of the product was not approved before September 24, 1984. Two (2) years, when added to the original expiration date of the patent (March 24, 1998), would result in the date March 24, 2000.

o. The earlier date, as determined in paragraphs m and n, is March 24, 2000.

Therefore, the length of extension of patent term claimed by applicant is two (2) years.

13. Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

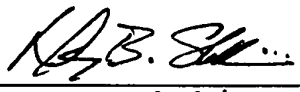
14. The prescribed fee for receiving and acting upon this application is to be charged to Deposit Account No. 13-3402, as authorized in the attached transmittal letter, which is submitted in triplicate.

15. All inquiries and correspondence relating to this application are to be directed to: Harry B. Shubin, Esq., Millen, White, Zelano, & Branigan, P.C., Arlington Courthouse I, 2200 Clarendon Boulevard, Suite 1201, Arlington, VA 22201, (703) 243-6333.

16. A duplicate of these application papers, certified as such, is being submitted herewith.

17. The requisite declaration pursuant to 37 C.F.R. §1.740(b) is attached.

Respectfully submitted,



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Filed: September 28, 1992

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 4,258,062	:	
Issued:	March 24, 1981	:	Box: Pat. Ext.
Inventors:	Rochus JONAS et al.	:	
		:	
For:	PHENOXY-AMINO PROPANOLS		

DECLARATION UNDER 37 C.F.R. §1.740(b)

Honorable Commissioner of
Patents and Trademarks
BOX PATENT EXTENSION
Washington, D.C. 20231

Sir:

The undersigned attorney for E. Merck GmbH, assignee of U.S. Patent No. 4,258,062 and the applicant submitting the attached Application for Extension of Patent Term Under 35 U.S.C. §156 with regard to U.S. Patent No. 4,357,324, hereby declares as follows:

1. THAT he is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in patent matters;

2. THAT he has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.740;

3. THAT he believes the patent is subject to extension pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710;

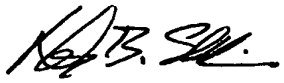
4. THAT he believes an extension of the length claimed is fully justified under 35 U.S.C. §156 and the applicable regulations; and

5. THAT he believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156 and 37 C.F.R. §1.720.

The undersigned hereby declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Further declarant sayeth not.

Signed this 28th day of September, 1992.



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Filed: September 28, 1992

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United States Patent [19]

Jonas et al.

[11] **4,258,062**

[45] **Mar. 24, 1981**

[54] **PHENOXY-AMINO-PROPANOLS**

[75] Inventors: **Rochus Jonas; Karl-Heinz Becker; Hans-Joachim Enenkel; Klaus Minck; Hans-Jochen Schliep**, all of Darmstadt, Fed. Rep. of Germany

[73] Assignee: **Merck Patent Gesellschaft mit beschränkter Haftung**, Darmstadt, Fed. Rep. of Germany

[21] Appl. No.: **43,925**

[22] Filed: **May 30, 1979**

Related U.S. Application Data

[62] Division of Ser. No. 839,487, Oct. 4, 1977, Pat. No. 4,171,370.

[30] **Foreign Application Priority Data**

Oct. 9, 1976 [DE] Fed. Rep. of Germany 2645710

[51] **Int. Cl.**[3] **A61K 31/135**; C07C 93/06

[52] **U.S. Cl.** **424/330**; 564/349

[58] **Field of Search** ..... 260/570.7 OH; 424/330

[56] **References Cited**

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3,275,654	9/1966	Wilhelm et al.	260/570.7 OH
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3,674,840	7/1972	Elof et al.	424/330
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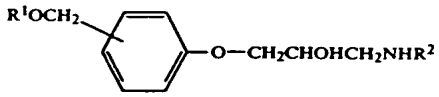
2065985	8/1977	Fed. Rep. of Germany	260/570.7 OH
4906M	4/1967	France	424/330
4905M	4/1967	France	424/330
44-10530	5/1969	Japan	260/570.7 OH

Primary Examiner—Allen J. Robinson

Attorney, Agent, or Firm—Millen & White

[57] **ABSTRACT**

New phenoxy-amino-propanols of formula



wherein R^1 is alkenyl, alkynyl, alkoxyalkyl or alkenyloxyalkyl with 2–6 C atoms in each case or cycloalkyl with 3–8 C atoms; and R^2 is alkyl or hydroxyalkyl with 1–6 C atoms in each case, cycloalkyl with 3–8 C atoms, aralkyl or aralkyl wherein the aryl radical is mono- to tri-substituted by alkyl, alkoxy, OH, F and/or Cl or mono-substituted by methylenedioxy, with a total of 7–15 C atoms in each case, and the physiologically acceptable acid addition salts thereof, exhibit various pharmacological properties including isoprenaline-antagonism on the heart rate and blood pressure.

9 Claims, No Drawings

Attachment A

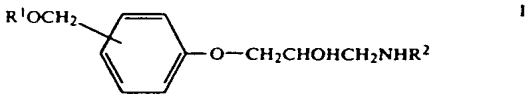
PHENOXY-AMINO-PROPANOLS

This is a division of application Ser. No. 839,487, filed Oct. 4, 1977, now U.S. Pat. No. 4,171,370.

SUMMARY OF THE INVENTION

This invention relates to new compounds and their physiologically acceptable salts.

In a composition aspect, this invention relates to compounds having the formula



I

wherein R^1 is alkenyl, alkynyl, alkoxyalkyl or alkenyloxyalkyl with 2–6 C atoms in each case or cycloalkyl with 3–8 C atoms; and R^2 is alkyl or hydroxyalkyl with 1–6 C atoms in each case, cycloalkyl with 3–8 C atoms or aralkyl or aralkyl wherein the aryl radical is mono- or tri-substituted by alkyl, alkoxy, OH, F, Cl or combinations thereof or monosubstituted by methylenedioxy, with a total of 7–15 C atoms in each case.

In another composition aspect, this invention relates to compositions containing the compounds for Formula I and pharmaceutically acceptable carriers.

In a method of use aspect, this invention relates to a method for obtaining pharmaceutical effects including isoprenaline-antagonism on the heart rate and blood pressure, which comprises administering a pharmaceutically effective amount of a compound of Formula I.

DETAILED DISCUSSION

In Formula I, the group R^1OCH_2— is preferably in the p- or o-position of the benzene ring; however, it can also be in the m-position.

When the radical R^1 is alkenyl, it is preferably straight-chained. Suitable radicals include allyl, vinyl, propenyl, isopropenyl, butenyl (for example, but-1-en-1-yl, but-1-en-2-yl, but-2-en-1-yl, but-2-en-2-yl, but-3-en-1-yl and but-3-en-2-yl), isobutenyl (for example 2-methyl-prop-2-en-1-yl), pentenyl (for example pent-2-en-1-yl) or hexenyl (for example hex-2-en-1-yl). Allyl is particularly preferred. The alkynyl groups are also preferably straight-chained and include propargyl, ethynyl, prop-1-yn-1-yl, butynyl (for example but-2-yn-1-yl), pentynyl (for example pent-2-yn-1-yl) or hexynyl (for example hex-2-yn-1-yl). Propargyl is particularly preferred. Alkoxy-alkyl groups are also preferably straight-chained, preferably alkoxyethyl (wherein the alkoxy group has 1–4 C atoms), in particular 2-methoxyethyl, 2-ethoxyethyl, 2-propoxyethyl or 2-isopropoxyethyl. Other suitable alkoxyalkyl groups include alkoxy-propyl, for example 2- or 3-methoxypropyl; alkoxybutyl, for example 2-, 3- or 4-methoxybutyl; and alkoxypentyl, for example 5-methoxypentyl. Alkenyloxyalkyl groups are preferably 2-alkenyloxyethyl and in particular 2-allyloxyethyl. Other suitable such groups include 2-vinyloxyethyl or 2-propenyloxyethyl, and also, for example, alkenyloxypropyl, such as 2- or 3-allyloxypropyl. Cycloalkyl groups are preferably cyclopentyl or cyclohexyl; but other suitable cycloalkyl groups include cyclopropyl, cyclobutyl, 1-, 2- or 3-methylcyclopentyl, 1-, 2-, 3- or 4-methylcyclohexyl, cycloheptyl and cyclooctyl.

When the radical R^2 is alkyl, it is preferably branched alkyl, in particular with 3 or 4 C atoms, such as isopropyl, isobutyl or tert-butyl. Other suitable alkyl groups include methyl, ethyl, n-propyl, n-butyl, sec-butyl, pentyl, such as 1-, 2- or 3-pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, such as 1-, 2- or 3-hexyl and isohexyl. Suitable hydroxyalkyls include for example: hydroxymethyl, 1- or 2-hydroxyethyl, 1-, 2- or 3-hydroxypropyl, 1-hydroxy-1-methyl-ethyl, 1-methyl-2-hydroxyethyl, 1-, 2-, 3- or 4-hydroxybutyl, 5-hydroxypentyl and 6-hydroxyhexyl. When R^2 is cycloalkyl, suitable groups are those indicated above for R^1.

When R^2 is aralkyl, it has 7–15, preferably 7–11 C atoms. The aryl group is a hydrocarbon. The preferred aralkyl is 2-phenylethyl. Other suitable groups include benzyl, 1-phenylethyl, 1-methyl-2-phenylethyl, 1,1-dimethyl-2-phenylethyl, 2-methyl-2-phenylethyl, 2,2-dimethyl-2-phenylethyl, 1,2-dimethyl-2-phenylethyl, 1-, 2- or 3-phenylpropyl, 1-methyl-3-phenylpropyl, 1-, 2-, 3- or 4-phenylbutyl, 1- or 2-naphthylmethyl, 2-(1-naphthyl)-ethyl or 2-(2-naphthyl)-ethyl. The alkyl group of the aralkyl preferably has from 1 to 4 C atoms.

The aryl radical of the aralkyl group can also be mono- to tri-substituted by alkyl, alkoxy, OH, F and/or Cl or monosubstituted by methylenedioxy. Suitable alkyl or alkoxy substituent groups have 1–8, preferably 1–4 C atoms. However, per above, the substituted aralkyl radical may not contain more than a total of 15 C atoms, preferably 7–11 C atoms. Suitable alkyl groups include in particular, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl and n-octyl. Suitable alkoxy groups include in particular, methoxy, and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, isopentyloxy, n-hexyloxy, n-heptyloxy and n-octyloxy.

The most preferred substituted aryl radicals are, alkoxyphenyl groups, such as o-, m- or p-methoxyphenyl; or o-, m- or p-ethoxyphenyl; dialkoxyphenyl, such as 2,3-, 2,4-, 2,5-, 2,6-, 3,5- or, particularly preferably 3,4-dimethoxyphenyl; trialkoxyphenyl, such as 3,4,5-trimethoxyphenyl; methylenedioxyphenyl, such as 3,4-methylenedioxyphenyl. Also preferred are for example, alkylphenyl, such as o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-isopropylphenyl or o-, m- or p-tert-butylphenyl; dialkylphenyl, such as 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl; trialkylphenyl, such as 2,4,6-trimethyl-phenyl or 2,6-dimethyl-4-tert-butylphenyl; o-, m- or p-hydroxyphenyl; dihydroxyphenyl, such as 3,4-dihydroxyphenyl; o-, m- or p-fluorophenyl and o-, m- or p-chlorophenyl. The aryl radicals can also carry two different substituents, such as 3-methoxy-4-hydroxyphenyl and 3-hydroxy-4-methoxyphenyl. 2-(3,4-dimethoxyphenyl)-ethyl is a particularly preferred substituted aralkyl radical. Further particularly preferred substituted aralkyl radicals are, for example, 2-(p-methoxyphenyl)-ethyl, 2-(3,4,5-trimethoxyphenyl)-ethyl and 2-(3,4-methylenedioxyphenyl)-ethyl.

This invention accordingly relates, in particular, to those compounds of Formula I in which at least one of the radicals R^1 and R^2 has one of the preferred meanings indicated above.

Contemplated classes of compounds within the scope of Formula I are those wherein:

(a) R^1 is alkenyl;

(b) R^1 is alkynyl;

(c) R^1 is alkoxyalkyl;

(d) R^1 is alkenyloxyalkyl;

(e) R^1 is cycloalkyl;
(f) R^2 is alkyl including each of (a)–(e);
(g) R^2 is hydroxyalkyl including each of (a)–(e);
(h) R^2 is cycloalkyl including each of (a)–(e);
(i) R^2 is aralkyl including each of (a)–(e);
(j) R^2 is substituted aralkyl including each of (a)–(e);
(k) R^2 is substituted aralkyl wherein the substituent is OH or alkoxy including each of (a)–(e);
(l) R^2 is substituted aralkyl wherein the substituent is F or Cl including each of (a)–(e);
(m) R^2 is substituted aralkyl wherein the substituent is methylenedioxy including each of (a)–(e); and
(n) R^2 is substituted aralkyl wherein the substituent is alkyl including each of (a)–(e).

Some preferred groups of compounds can be expressed by the following partial Formulae Ia to Ip which correspond to the Formula I and wherein the radicals not described in more detail are as defined in Formula I, but wherein

in Ia, R^1 is alkenyl or alkynyl with 2–6 C atoms in each case;

in Ib, R^1 is alkoxyalkyl or alkenyloxyalkyl with 2–6 C atoms in each case;

in Ic, R^1 is cycloalkyl with 3–8 C atoms;

in Id, R^1 is allyl, propargyl, 2-alkoxyethyl with 3–5 C atoms, 2-allyloxyethyl or cyclopentyl;

in Ie, R^2 is alkyl or hydroxyalkyl with 1–6 C atoms ine each case or cycloalkyl with 3–8 C atoms;

in If, R^2 is unsubstituted aralkyl or aralkyl wherein the aryl radical is mono- or tri-substituted by alkyl, alkoxy, OH, F and/or Cl or is mono-substituted by methylenedioxy, with a total of 7–15 C atoms in each case;

in Ig, R^2 is isopropyl, tert-butyl, 2-phenylethyl, 1,1-dimethyl-2-phenylethyl or 2-(3,4-dimethoxyphenyl)-ethyl;

in Ih, R^2 is isopropyl or tert-butyl;

in Ii, R^2 is 2-phenylethyl or 2-(3,4-dimethoxyphenyl)-ethyl;

in Ij, R^1 is alkenyl or alkynyl with 2–6 C atoms in each case and R^2 is alkyl with 1–6 C atoms, phenylalkyl with 7–10 C atoms or phenylalkyl wherein phenyl is mono- to tri-substituted by methoxy or mono-substituted by methylenedioxy, with a total of 9–13 C atoms;

in Ik, R^1 is allyl, propargyl, 2-alkoxyethyl with 3–5 C atoms, 2-allyloxyethyl or 2-cyclopentyl and R^2 is isopropyl, tert-butyl, 2-phenylethyl, 1,1-dimethyl-2-phenylethyl or 2-(3,4-dimethoxyphenyl)-ethyl;

in Il, R^1 is allyl or propargyl and R^2 is isopropyl, tert-butyl, 2-phenylethyl, 1,1-dimethyl-2-phenylethyl or 2-(3,4-dimethoxyphenyl)-ethyl;

in Im, R^1 is allyl or propargyl and R^2 is 2-(3,4-dimethoxyphenyl)-ethyl;

in In, R^1 is alkoxyalkyl or alkenyloxyalkyl with 2–6 C atoms in each case or cycloalkyl with 3–8 C atoms and R^2 is alkyl with 1–6 C atoms, phenylalkyl with 7–10 C atoms or phenylalkyl wherein phenyl is mono- to tri-substituted by methoxy or mono-substituted by methylenedioxy, with a total of 9–13 C atoms;

in Io, R^1 is 2-alkoxyethyl with 3–5 C atoms, 2-allyloxyethyl or cyclopentyl and R^2 is isopropyl, tert-butyl, 2-phenylethyl, 1,1-dimethyl-2-phenylethyl or 2-(3,4-dimethoxyphenyl)-ethyl; and

in Ip, R^1 is 2-alkoxyethyl with 3–5 C atoms or 2-allyloxyethyl and R^2 is isopropyl or tert-butyl.

The compounds of Formula I possess at least one asymmetric C atom and can contain further asymmetric C atoms in the substituents R^1 and R^2. They can thus exist in the racemic or in the optically active form. They are generally obtained as racemates in synthesis.

The compounds of Formula I can be prepared by conventional methods which are described in the literature, for example, in standard works such as Houben-Weyl, *Methoden der Organischen Chemie*, Georg-Thieme-Verlag, Stuttgart; and *Organic Reactions*, John Wiley and Sons, Inc., New York. Suitable reaction conditions are known and details can be determined by conventional considerations. Use can also be made of conventional variations which are not discussed in detail herein.

Such processes for the preparation of the phenoxyamino-propanols of Formula I and their physiologically acceptable acid addition salts, include:

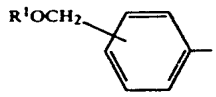
(1) reacting a compound of Formula II

$$Ar—O—CH_2—CHQ—CH_2Y \qquad II$$

with a compound of Formula III

$$Z—R^2 \qquad III$$

wherein Ar is



one of the radicals Y and Z is NH_2 and the other is X; Q is OH or, together with X, is an oxygen atom; X is Hal, OH, a functionally modified OH group or (in II), together with Q, is an oxygen atom; Hal is Cl, Br or I; and R^1 and R^2 are as defined above;

(2) reacting a phenol of Formula IV

$$Ar—OH \qquad IV$$

wherein Ar is as defined above, with an aminoalcohol of Formula V

$$X—CH_2CHOHCH_2NHR^2 \qquad V$$

wherein R^2 and X are as defined above;

(3) reacting a compound of Formula VI

$$Ar—O—CH_2—W \qquad VI$$

wherein W is a radical which can be reduced to the group —CHOH—CH_2—NHR^2 and Ar and R^2 are as defined above, with a reducing agent; and

(4) treating a compound of the Formula I which, however, has one or more group(s) which can be split off solvolytically or hydrogenolytically in place of one or more of its H atoms, with a solvolyzing or hydrogenolyzing agent.

The physiologically acceptable acid addition salts are prepared by treating a resulting base of Formula I with an acid.

Some of the starting materials used in preparation of the compounds of Formula I are known and some are new. The new starting materials can be prepared by conventional processes in analogous manner to those used to prepare the known starting materials. If desired,

the starting materials can also be formed in situ without being isolated from the reaction mixture but rather immediately reacted to produce the compounds of Formula I.

In the following text, the radicals R^1, R^2, Ar, Hal, Q, W, X, Y and Z are as defined for Formulae I to VI, unless otherwise expressly indicated.

The radical X can be present in the starting materials of Formulae II, III and V. X is preferably Cl or Br, but I, OH or a functionally modified OH group are also suitable. Suitable functionally modified OH groups, in particular, include reactive esterified OH groups, for example alkylsulphonyloxy preferably with 1-6 C atoms, such as methanesulphonyloxy, or arylsulphonyloxy preferably with 6-10 C atoms, such as benzenesulphonyloxy, p-toluenesulphonyloxy or 1- or 2-naphthalenesulphonyloxy.

In general, the starting materials of Formula II are new. They can be obtained, for example, by reacting phenols of the Formula Ar—OH (IV) with compounds of the Formula $X—CH_2—CHQ—CH_2Y$ (for example epichlorohydrin or epibromohydrin). Primary amines of Formula II ($Y=NH_2$) can be prepared, for example, by reacting epoxides of Formula II (i.e., Q and Y are together an oxygen atom) with ammonia or with benzylamine and subsequently removing the benzyl group hydrogenolytically.

Generally, starting materials of Formula III are known. The Formula III amines ($Z=NH_2$) can be obtained from the corresponding halogen compounds of Formula III (Z=Hal) by reaction with ammonia or by reaction with benzylamine and subsequent hydrogenolytic splitting-off of the benzyl group. Compounds of the Formulae II and III in which the radicals Y or Z are functionally modified OH groups can be obtained by functional modification of the corresponding alcohols, for example by reaction with alkyl- or aryl-sulphonyl halides in the presence of pyridine.

Generally, the phenols of Formula IV are new. They can be obtained by reacting o-, m- or p-hydroxybenzyl alcohol with compounds of the formula $R^1—X$, preferably by etherification with the corresponding alcohols of the formula $R^1—OH$, which as a rule are known. Aminoalcohols of Formula V can be prepared, for example, by reacting compounds of the formula $X—CH_2—CHQ—CH_2Y$ (preferably epoxides, such as epichlorohydrin) with amines of Formula III ($Z=NH_2$).

In the starting materials of Formula VI, the substituent W is a group which can be reduced to the group $—CHOH—CH_2—NHR^2$, preferably one of the groups $—CO—CH_2—NHR^2$ ($=W^1$), $—CHOH—CH=NR^2$ ($=W^2$), $—CHOH—CH_2—N=R^3$ ($=W^3$; wherein R^3 is an alkylidene, hydroxyalkylidene or cycloalkylidene group or an aralkylidene group which is unsubstituted or which has aryl substitution as indicated in the definition of R^2), or $—CHOH—CH_2—NH—R^4$ ($=W^4$; wherein R^4 is a radical which can be reduced to the group R^2, for example a radical corresponding to the group R^2 but which contains an additional C—C bond or an oxygen atom instead of two hydrogen atoms, for example alkanoyl, oxoalkyl, alkenyl, hydroxyalkanoyl or hydroxyalkenyl with up to 6 C atoms in each case, oxocycloalkyl or cycloalkenyl with 3-8 C atoms or aryl-alkanoyl, aryl-oxoalkyl or arylalkenyl, unsubstituted or having aryl groups substituted as indicated in the definition of R^2, with a total of 7-15 C atoms in each case).

The compounds of the Formula VI can be obtained, for example, by reacting the phenols of Formula IV with compounds of the formula $X—CH_2—W$. Furthermore, the starting materials of Formula VI ($W=W^1$) can be obtained by reacting compounds of the formula $Ar—O—CH_2—CO—CH_2—X$ with amines of the formula $R^2—NH_2$; the compounds of the Formula VI ($W=W^2$) can be obtained by reacting aldehydes of the formula $Ar—O—CH_2—CHOH—CHO$ with amines of the formula $R^2—NH_2$; the compounds of the Formula VI ($W=W^3$) can be obtained by reacting amines of the formula $Ar—O—CH_2—CHOH—CH_2NH_2$ with aldehydes of the formula $R^3=O$; and the compounds of the Formula VI ($W=W^4$) can be obtained by reacting compounds of the formula $Ar—O—CH_2—CHOH—CH_2—X$ with amines of the formula $R^4—NH_2$.

The compounds of Formula I are preferably prepared by reacting compounds of Formula II with compounds of Formula III. On the one hand, it is possible to react epoxides of Formula II (Q and Y together are an oxygen atom), halogeno-alcohols of the Formula II (Q=OH, Y=Hal) or diols or their functional derivatives of the Formula II (Q=OH, Y=OH or functionally modified OH) with amines of the Formula III ($Z=NH_2$); and on the other hand it is possible to react amines of the Formula II (Q=OH, $Y=NH_2$) with compounds of the Formula III (Z=X). The reaction of the epoxides with amines of the formula $R^2—NH_2$ is preferred.

The reaction of compounds of Formula II with compounds of Formula III can be optionally carried out in the presence of an additional inert solvent, at temperatures between about 0° and 200° C., preferably between about 20° and 120° C. Suitable inert solvents are conventional for amination reactions of this type, and are known, from the literature, for example water; alcohols, such as methanol, ethanol, isopropanol or n-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; hydrocarbons, such as benzene, toluene or xylene; halogenated hydrocarbons, such as dichloromethane, chloroform or trichloroethylene; nitriles, such as acetonitrile; amides, such as dimethylformamide (DMF); or sulphoxides, such as dimethylsulphoxide (DMSO). Mixtures of these solvents can also be used. The amines are preferably used in a molar ratio of at least 1:1 or in excess. If they are used in excess, they can simultaneously serve as the solvent. It is also possible to add an additional base, for example an inorganic base, such as sodium or potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate or potassium bicarbonate. If the starting compounds have a structure such that one mole of acid is split off during the reaction (for example if halohydrins are used, so that hydrogen halide is split off), it is preferred to employ either an additional base or an excess of the amine.

If X is an OH group, or also an alkyl- or arylsulphonyloxy group, it may also be advisable to add an acid catalyst, for example an inorganic acid (such as sulphuric acid, polyphosphoric acid, hydrobromic acid or hydrochloric acid) and/or an organic acid (such as formic, acetic, propionic or p-toluenesulphonic acid). An excess of the acid can also simultaneously serve as the solvent.

The required reaction times are between about 10 minutes and 7 days, depending on the starting materials and the reaction temperature. It is also possible to carry out the process under pressure (up to about 200 atmospheres) and thereby accelerate the reaction.

The compounds of Formula I can also be obtained by reacting the phenols of Formula IV with the aminoalcohols of Formula V. Optionally, the phenol IV can first be converted into a salt, in particular a metal salt, for example an alkali metal salt (Li, Na or K salt). This can be accomplished by reacting the phenol with a reagent which forms metal salts, for example an alkali metal (e.g., Na), an alkali metal hydride or amide (for example, LiH or NaH or $NaNH_2$ or KNH_2), an alkali metal alcoholate (wherein the alcohol portion preferably has 1–4 C atoms, for example lithium methylate, ethylate or tert-butylate, sodium methylate, ethylate or tert-butylate or potassium methylate, ethylate or tert-butylate), an organometallic compound (for example, butyllithium, phenyllithium or phenylsodium) or a metal hydroxide, carbonate or bicarbonate (for example, of Li, Na, K or Ca). The preparation of the phenolate is advantageously carried out in the presence of a solvent or solvent mixture. Suitable solvents include, for example, hydrocarbons (such as hexane, benzene, toluene or xylene), ethers (for example, diethyl ether, diisopropyl ether, THF, dioxane or diethylene glycol dimethyl ether), amides (for example, DMF), alcohols (for example, methanol or ethanol) or ketones (for example, acetone or butanone). The phenol IV or its salt is preferably reacted with compound V in the presence of a diluent, for example, the solvent which has been used for the preparation of the salt, which, however, can be replaced by or diluted with another solvent. Generally, the reaction is carried out at temperatures between about −20° and 150° C., preferably between 20° and 120° C.

The phenolate can also be formed in situ. In this case, the phenol IV and compound V are allowed to react with one another in the presence of a base. A particularly preferred method is to heat the compounds IV and V together with an alcoholic-aqueous sodium hydroxide solution for about 5 to 15 hours.

Furthermore, it is possible to reduce a compound of Formula VI in order to prepare the compounds of Formula I. Suitable reducing agents include, for example, complex metal hydrides. The compounds of Formula VI can also be reduced with the aid of catalytically activated or nascent hydrogen. Among the complex metal hydrides, sodium borohydride and lithium aluminum hydride are preferred. The reaction is preferably carried out in one of the conventional solvents, with $NaBH_4$ preferably in an alcohol, such as methanol or ethanol, and with $LiAlH_4$ preferably in an ether, such as diethyl ether or di-n-butyl ether, THF or ethylene glycol dimethyl ether. Suitable reaction temperatures are generally between about −80° and 150° C., preferably between 15° C. and the boiling point of the solvent.

Suitable catalysts for the catalytic hydrogenation include, for example nickel and cobalt catalysts, and noble metal and mixed catalysts, such as copper/-chromium oxide. The noble metal catalysts can be supported (for example platinum- or palladium-on-charcoal or palladium-on-calcium carbonate or -strontium carbonate), or be in the form of oxide catalysts (for example platinum oxide) or finely divided metal catalysts. Nickel and cobalt catalysts are preferably employed as Raney metals. Nickel can also be used on kieselghur or pumice supports.

The hydrogenation can be carried out at room temperature under normal pressure, or also at elevated temperature and/or under increased pressure. The reaction is preferably carried out under pressures between 1 and 100 atmospheres and at temperatures between −80° and +150° C., especially between room temperature and +100° C. The reaction is carried out in acidic, neutral or basic conditions and in the presence of a solvent, such as water, methanol, ethanol, isopropanol, n-butanol, ethyl acetate, dioxane acetic acid or THF. Mixtures of these solvents can also be used. Raney metals are preferred catalysts for the catalytic hydrogenation of the aminoketones of Formula VI (W=W^1).

If nascent hydrogen is used as the reducing agent, it can be produced, for example, by treating metals with acids or bases. For example, mixtures of zinc and acid or alkali metal hydroxide solution; of iron and hydrochloric acid or acetic acid; or of tin and hydrochloric acid can be used. The use of sodium or another alkali metal in an alcohol, such as ethanol, isopropanol, butanol or amyl or isoamyl alcohol, or phenol is also suitable. Furthermore, an aluminum/nickel alloy in an alkaline-aqueous solution, optionally with the addition of ethanol, can be used. Sodium amalgam and aluminum amalgam in aqueous-alcoholic or aqueous solutions are also suitable for producing the nascent hydrogen. The reaction can also be carried out in a heterogeneous phase, an aqueous phase and a benzene or toluene phase being preferably used. Suitable reaction temperatures include those between room temperature and the boiling point of the solvent.

Moreover, the phenoxy-amino-propanols of Formula I can be obtained by solvolysis or hydrogenolysis of a compound which has Formula I but which contains one or more group(s) which can be split off solvolytically or hydrogenolytically in place of one or more H atoms.

Suitable starting materials for this process variant include, in particular, compounds of the formula $Ar—O—CH_2—CHOR^5—CH_2—NR^2R^6$ (VII), wherein the radical R^5 is H or a hydroxyl protecting group and the radical R^6 is H or an amino protecting group; but the radicals R^5 and R^6 cannot simultaneously be H; and Ar and R^2 are as defined above.

The expressions "hydroxyl protecting group" and "amino protecting group" are well known and refer to groups which are suitable for protecting (blocking) a hydroxyl group or an amino group from chemical reactions but which can be easily removed after the desired chemical reaction has been carried out at other positions in the molecule. Since these protecting groups are later removed, their nature and size is in other respects not critical. However, R^5 and/or R^6 are preferably acyl with 1–20, in particular 1–8 C atoms (for example alkanoyl, such as acetyl; aroyl such as benzoyl; aralkanoyl, such as phenylacetyl; alkoxycarbonyl, such as methoxycarbonyl; aralkyloxycarbonyl, such as benzyloxycarbonyl; or arylsulphonyl, such as p-toluenesulphonyl); or optionally substituted benzyl (for example benzyl, p-nitrobenzyl or triphenylmethyl).

Solvolysis of these compounds is preferably effected by the action of a solvent such as water (hydrolysis) or of an alcohol with preferably 1–4 C atoms (alcoholysis) in the presence of an acidic or basic catalyst. Suitable such catalysts include mineral acids, such as sulphuric acid or hydrochloric acid; metal hydroxides, such as sodium, potassium, calcium, barium, lead or silver hydroxide; or metal or ammonium salts, such as sodium or potassium carbonate or ammonium chloride. Methanol, ethanol or isopropanol are preferably used as alcohols. Mixtures of water with one of these alcohols can also be used. The solvolysis is preferably carried out at temperatures between about 0° and about 120° C.

Hydrogenolysis can be carried out, for example, under the conditions described above for catalytic hydrogenation, preferably on a Raney nickel catalyst at temperatures between about 20° and 100° C. and under pressures between 1 and 10 atmospheres.

A base of Formula I can be converted into its associated acid addition salts by reaction with a suitable acid which produces a physiologically acceptable salt. Suitable salts include those of inorganic acids such as sulphuric acid, nitric acid, hydrogen halide acids, such as hydrochloric acid or hydrobromic acid, and phosphoric acid, such as orthophosphoric acid, and organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic or sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenyl-propionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethane-sulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid and naphthalene-mono- and di-sulphonic acids. If desired, the free bases of Formula I can be liberated from such salts by treatment with strong bases, such as sodium hydroxide or potassium hydroxide or sodium carbonate or potassium carbonate.

The compounds of Formula I are usually obtained in racemic form. When the compounds have two or more centers of asymmetry, they are generally obtained in synthesis as mixtures of racemates, from which the individual racemates can be isolated and obtained in pure form, for example by several recrystallizations from suitable solvents.

The resulting racemates can be mechanically or chemically resolved into their optical antipodes by conventional methods. Preferably, diastereomers are formed from the racemic mixture by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the D- and L- forms of tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, β-camphorsulphonic acid, mandelic acid, malic acid or lactic acid. Furthermore, it is also possible to obtain optically active compounds by using starting materials which are already optically active in the foregoing preparative methods.

The compounds of Formula I possess very valuable pharmacological properties for mammals, including humans, and are well tolerated. They primarily exhibit isoprenaline-antagonism on the heart rate and blood pressure, for example in guinea pigs, cats or dogs. This effect can be determined, for example, by the method described in detail in German Auslegeschrift No. 1,493,564. Some of the compounds also exhibit a cardioselective action. Additionally, they can be used to lower cholesterol and triglyceride levels as can be determined in rats in accordance with the methods described by Levine and co-workers (*Automation in Analytical Chemistry*, Technicon Symposium, 1967, Mediad, New York, pages 25–28) and by Noble and Campbell (Clin. Chem. 16 (1970), pages 166–170). Furthermore, the products exert effects on the central nervous system; inhibit thromobocyte aggregation, display antiarrhythmic effects and inhibit lipolysis, all of which can be conventionally determined. The compounds thus exhibit a very broad spectrum of activity.

The compounds can accordingly be employed as medicaments in both human and veterinary medicine, in particular for the prophylaxis and treatment of cardiac, circulatory and vascular diseases, such as angina pectoris and coronary infarction as well as symptoms connected with these, e.g. hypertonia and arrhythmic effects.

The compounds are adrenergic β-receptor blockers similar to propranolol. In contrast to propranolol, however, they do not show strong undesired broncho constrictoric effects but are cardioselective β_1-blockers.

Furthermore, they can be used as intermediate products for the preparation of other medicaments.

The compounds of Formula I and their physiologically acceptable salts can be prepared for pharmaceutical use by formulation in a suitable dosage form together with at least one excipient or auxiliary and, if desired, together with one or more other active compound(s). The formulations thus obtained can be employed in human or veterinary medicine. Suitable excipients include conventional organic or inorganic substances used for enteral (for example oral) or parenteral administration or topical application which do not react with the new compounds. These include, for example, water, vegetable oils, benzyl alcohols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates, such as lactose or starch, magnesium stearate, talc or petroleum jelly. Tablets, dragees, capsules, syrups, elixirs, drops etc. can be used for oral administration; suppositories can be used for rectal administration; solutions, preferably oily or aqueous solutions, and also suspensions, emulsions or implantates can be used for parenteral administration; and ointments, creams or powders can be used for topical application. The new compounds can also be lyophilised and the resulting lyophilisates can be used, for example, for the preparation of injection formulations. All these formulations can be sterilized and/or can contain auxiliaries, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, dyestuffs, flavoring agents and/or aroma generating substances. If desired, they can also contain one or more other active compounds, for example one or more vitamins.

Generally, the compounds of this invention are administered in a manner analogous to that known for commercially available cardiac and circulatory formulations, in particular β-receptor blockers, preferably in dosages between about 0.5 and 200 mg, in particular between 2 and 50 mg, per dosage unit. The daily dosage is preferably between about 0.01 and 4 mg/kg of body weight. However, the specific dose suitable for an individual patient depends on the usual diverse factors, for example the activity of the specific compound employed, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, medicament combination and severity of the particular disease for which therapy is given. Oral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Each of the compounds of formula I mentioned in the examples is particularly suitable for the preparation of pharmaceutical formulations.

In the examples, the "customary work up" refers to the following procedure: water is added, if necessary; the mixture is extracted with an organic solvent, such as ethyl acetate, chloroform or dichloromethane, and separated; the organic phase is dried over sodium sulphate and filtered; the filtrate is evaporated; and the residue is purified by chromatography and/or crystallization.

A "fumarate" is the neutral salt produced from 2 moles of base and 1 mole of fumaric acid.

EXAMPLE 1

A mixture of 22 g. of crude oily 1-(p-allyloxymethyl-phenoxy)-2,3-epoxypropane [obtainable by heating p-hydroxybenzylalcohol with allyl alcohol to 150° for 4 hours and reacting the resulting p-allyloxymethyl-phenol (boiling point 123°–125°/0.01 mm. Hg) with epichlorohydrin] and 20 g. of 3,4-dimethoxyphenylethylamine was stirred for 12 hours at 25°. 60 ml. of ethanol were added to the resulting 1-(p-allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol and the precipitate was filtered off and recrystallized from isopropanol. Hydrochloride, melting point 126°.

EXAMPLES 2 TO 27

Analogously to Example 1, reacting
1-(o-allyloxymethyl-phenoxy)-2,3-epoxypropane,
1-(m-allyloxymethyl-phenoxy)-2,3-epoxypropane,
1-(p-allyloxymethyl-phenoxy)-2,3-epoxypropane,
1-(o-proparglyoxymethyl-phenoxy)-2,3-epoxypropane,
1-(o-2-methoxyethoxymethyl-phenoxy)-2,3-epoxypropane,
1-(o-2-isopropoxyethoxymethyl-phenoxy)2,3-epoxypropane,
1-(p-2-isopropoxyethoxymethyl-phenoxy)-2,3-epoxypropane,
1-(o-2-allyloxyethoxymethyl-phenoxy)-2,3-epoxypropane or
2-(o-cyclopentoxymethyl-phenoxy)-2,3-epoxypropane (each obtainable from o-, m- or p-hydroxybenzyl alcohol by etherification with the corresponding alcohol and subsequent reaction with epichlorohydrin) with 2-phenylethylamine, 1,1-dimethyl-2-phenylethylamine or 2-(3,4-dimethoxyphenyl)-ethylamine produced:

2. 1-(o-Allyloxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol, fumarate, m.p. 93°.
3. 1-(o-Allyloxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
4. 1-(o-Allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, fumarate, m.p. 110°.
5. 1-(m-Allyloxymethyl-phenoxy)-(2-phenylethylamino)-propan-2-ol.
6. 1-(m-Allyloxymethyl-phenoxy)-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
7. 1-(m-Allyloxymethyl-phenoxy)-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
8. 1-(p-Allyloxymethyl-phenoxy)-3-(2-phenylethylamino)propan-2-ol, hydrochloride, m.p. 150°.
9. 1-(p-Allyloxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol, hydrochloride, m.p. 142°.
10. 1-(o-Propargyloxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol, fumarate, m.p. 85°.
11. 1-(o-Propargyloxymethyl-phenxoy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
12. 1-(o-Propargyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, fumarate, m.p. 115°.
13. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol.
14. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
15. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
16. 1-(o-2-Isopropoxyethoxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol.
17. 1-(o-2-Isopropoxyethoxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
18. 1-(o-2-Isopropoxyethoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, fumarate, m.p. 116°.
19. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol.
20. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
21. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, hydrochloride, m.p. 126°.
22. 1-(o-2-Allyloxyethoxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol.
23. 1-(o-2-Allyloxyethoxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol, fumarate, m.p. 115°.
24. 1-(o-2-Allyloxyethoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, fumarate, m.p. 95°.
25. 1-(o-Cyclopentoxymethyl-phenoxy)-3-(2-phenylethylamino)-propan-2-ol.
26. 1-(o-Cyclopentoxymethyl-phenoxy)-3-(1,1-dimethyl-2-phenylethylamino)-propan-2-ol.
27. 1-(o-Cyclopentoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, hydrochloride, m.p. 127°.

EXAMPLE 28

A solution of 22 g. of 1-(o-allyloxymethyl-phenoxy)-2,3-epoxypropane and 33 ml. of isopropylamine in 45 ml. of ethanol was allowed to stand for 15 hours at 20°. The solution was evaporated and the residue dissolved in ethyl acetate and extracted wiht dilute hydrochloric acid. The aqueous phase was rendered alkaline and worked up in the customary manner. This produced 1-(o-allyloxymethyl-phenoxy)-3-isopropylaminopropan-2-ol; fumarate, m.p. 106°.

EXAMPLES 29 to 54

Analogously to Example 28, the epoxides indicated in Examples 2 to 27 and isopropylamine, tert.-butylamine or 1-methyl-2-hydroxyethylamine produced:

29. 1-(o-Allyloxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol.
30. 1-(o-Allyloxymethyl-phenoxy)-3-(1-methyl-2-hydroxyaethylamino)-propan-2-ol.
31. 1-(m-Allyloxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 90°.
32. 1-(m-Allyloxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol.
33. 1-(m-Allyloxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamno)-propan-2-ol.
34. 1-(p-Allyloxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 103°.
35. 1-(p-Allyloxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol, fumarate, m.p. 148°.

36. 1-(p-Allyloxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamino)-propan-2-ol.
37. 1-(o-Propargyloxymethyl-phenoxy)-3-isopropylaminopropan-2-ol, fumarate, m.p. 177°.
38. 1-(o-Propargyloxymethyl-phenoxy)-3-tert.-butylaminopropan-2-ol, fumarate, m.p. 166°.
39. 1-(o-Propargyloxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamino)-propan-2-ol.
40. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-isopropylaminopropan-2-ol, fumarate, m.p. 95°.
41. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol, fumarate, m.p. 115°.
42. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamino)-propan-2-ol.
43. 1-(o-2-Isopropoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 90°.
44. 1-(o-2-Isopropoxyethoxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol, fumarate, m.p. 132°.
45. 1-(o-2-Isopropoxyethoxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamino)-propan-2-ol.
46. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 100°.
47. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol, hemifumarate, m.p. 105°.
48. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamino)-propan-2-ol.
49. 1-(o-2-Allyloxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 92°.
50. 1-(o-2-Allyloxyethoxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol, fumarate, m.p. 122°.
51. 1-(o-2-Allyloxyethoxymethyl-phenoxy)-3-(1-methyl-2-hydroxyethylamino)-propan-2-ol.
52. 1-(o-Cyclopentoxymethyl-phenoxy)-3-isopropylaminopropan-2-ol, hydrochloride, m.p. 124°.
53. 1-(o-Cyclopentoxymethyl-phenoxy)-3-tert.-butylaminopropan-2-ol, hydrochloride, m.p. 128°.
54. 1-(o-Cyclopentoxymethyl-phenoxy)-3-(1-methyl-2-hydroxy-ethylamino)-propan-2-ol.

EXAMPLES 55 TO 73

Analogously to Example 28, reactive 1-(o-2-methoxyethoxymethyl-phenoxy)-2,3-epoxypropane with the corresponding amines produced:

55. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-methylaminopropan-2-ol.
56. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-hexylamino)-propan-2-ol.
57. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(3-hydroxy-2-hexylamino)-propan-2-ol.
58. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-cyclopropylaminopropan-2-ol.
59. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-cyclopentylaminopropan-2-ol.
60. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-cyclohexylaminopropan-2-ol.
61. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-cyclooctylaminopropan-2-ol.
62. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-benzylaminopropan-2-ol.
63. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-p-tolylethylamino)-propan-2-ol.
64. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(1-methyl-3-phenyl-propylamino)-propan-2-ol.
65. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-p-methoxyphenylethylamino)-propan-2-ol.
66. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-[2-(3,4,5-trimethoxyphenyl)-ethylamino]-propan-2-ol.
67. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-p-hydroxyphenyl-ethylamino)-propan-2-ol.
68. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-p-fluorophenylethylamino)-propan-2-ol.
69. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-(2-p-chlorophenyl-ethylamino)-propan-2-ol.
70. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-[2-(3,4-methylenedioxyphenyl)-ethylamino]-propan-2-ol.
71. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-[2-(3-methoxy-4-hydroxyphenyl)-ethylamino]-propan-2-ol.
72. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-[1,1-dimethyl-2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
73. 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-[1,1-dimethyl-4-(3,4,5-trimethoxyphenyl)-butylamino]-propan-2-ol.

EXAMPLE 74

A mixture of 25.7 g. of 1-chloro-3-(p-allyloxymethyl-phenoxy)-propan-2-ol and 50 g. of 2-(3,4-dimethoxyphenyl)-ethylamine was heated to 100° for 18 hours, cooled and worked up in the customary manner. This produced 1-(p-allyloxy-methylphenoxy)-3-[2-(3,4-dimethoxyphenyl)ethylamino]-propan-2-ol. Hydrochloride, m.p. 126°.

EXAMPLES 75 TO 83

Analogously to Example 74, reacting
1-chloro-3-(p-vinyloxymethyl-phenoxy)-propan-2-ol,
1-chloro-3-(p-2-hexen-1-yl-oxymethyl-phenoxy)-propan-2-ol,
1-chloro-3-(p-ethinyloxymethyl-phenoxy)-propan-2-ol,
1-chloro-3-(p-5-hexin-1-yl-oxymethyl-phenoxy)-propan-2-ol,
1-chloro-3-(p-2-butoxyethoxymethyl-phenoxy)-propan-2-ol,
1-chloro-3-(p-2-vinyloxyethoxymethyl-phenoxy)-propan-2-ol,
1-chloro-3-[p-2-(2-buten-1-yloxy)-ethoxymethyl-phenoxy]-propan-2-ol.
1-chloro-3-(p-cyclopropoxymethyl-phenoxy)-propan-2-ol or 1-chloro-3-(p-cyclohexyloxymethyl-phenoxy)-propan-2-ol with 2-(3,4-dimethoxyphenyl)-ethylamine produced:

75. 1-(p-Vinyloxymethylphenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
76. 1-(p-2-Hexen-1-yloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
77. 1-(p-Ethinyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
78. 1-(p-5-Hexin-1-yloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
79. 1-(p-2-Butoxyethoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
80. 1-(p-2-Vinyloxyethoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
81. 1-[p-2-(2-Buten-1-yloxy)-ethoxymethyl-phenoxy]-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
82. 1-(p-Cyclopropoxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.
83. 1-(p-Cyclohexyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.

EXAMPLE 84

A mixture of 22.3 g. of 1-(p-allyloxymethyl-phenoxy)-3-amino-propan-2-ol [obtainable by reacting 1-(p-allyloxymethylphenoxy)-2,3-epoxypropane with NH_3],

13. 8 g. of potassium carbonate, 27 g. of 2-(3,4-dimethoxyphenyl)-ethyl bromide and 100 ml. of n-butanol was boiled for 24 hours, with stirring. The mixture was filtered, the filtrate evaporated and the residue worked up in the customary manner to give 1-(p-allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, hydrochloride, m.p. 126°.

EXAMPLE 85

A mixture of 16.4 g. of p-allyloxymethyl-phenyl, 27.4 g. of 1-chloro-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol [obtainable from epichlorohydrin and 2-(3,4-dimethoxyphenyl)-ethylamine], 8 g. of sodium hydroxide, 400 ml. of ethanol and 20 ml. of water was heated to 100° for 10 hours. The mixture was evaporated to dryness, the residue treated with dilute hydrochloric acid and ethyl acetate and separated and the aqueous phase rendered alkaline with sodium hydroxide solution and worked up in the customary manner to give 1-(p-allyloxymethylphenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, hydrochloride, m.p. 126°.

EXAMPLE 86

A mixture of 39.9 g. of 1-(p-allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-acetone (obtainable from p-allyloxymethylphenol and 1-bromo-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-one), 4 g. of $NaBH_4$ and 2 l. of methanol was stirred at 25° for 3 hours. It was worked up in the customary manner to give 1-(p-allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, hydrochloride, m.p. 126°.

EXAMPLE 87

A solution of 42.8 g. of N-(2-hydroxy-3-o-cyclopentyloxymethyl-phenoxy-propyl)-3,4-dimethoxy-phenylacetamide [obtainable from 3,4-dimethoxy-phenylacetyl chloride and 1-(o-cyclopentyloxymethyl-phenoxy)-3-amino-propan-2-ol] in 600 ml. of THF was added dropwise to a suspension of 10 g. of $LiAlH_4$ in 500 ml. of absolute ether, with stirring. The mixture was subsequently boiled for 20 hours and worked up in the customary manner to give 1-(o-cyclopentyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol, hydrochloride, m.p. 127°.

EXAMPLE 88

A solution of 10 g. of 1-(p-2-isopropoxyethoxymethylphenoxy)-3-isopropylideneamino-propan-2-ol [obtainable by reacting 1-(p-2-isopropoxyethoxymethyl-phenoxy)-2,3-epoxypropane with ammonia to give 1-(p-2-isopropoxyethoxymethylphenoxy)-3-amino-propan-2-ol and subsequently reacting this with acetone] in 250 ml. of ethanol was hydrogenated on 0.5 g. of Raney nickel at 25° under 1 atmosphere of pressure until 1 equivalent of H_2 had been absorbed. The mixture was filtered and the filtrate evaporated to give 1-(p-2-isopropoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 100°.

EXAMPLE 89

10 g. of N-[2-hydroxy-3-(p-2-isopropoxyethoxymethylphenoxy)-propyl]-N-isopropyl-acetamide [obtainable by reacting Na p-(2-isopropoxyethoxymethyl)-phenolate with N-(2-hydroxy-3-bromo-propyl)-N-isopropyl-acetamide] were boiled for 4 hours with 250 ml. of 20% hydrochloride acid. The mixture was evaporated and worked up in the customary manner to give 1-(p-2-isopropoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, fumarate, m.p. 100°.

EXAMPLE 90

10 g. of 1-(o-2-methoxyethoxymethyl-phenoxy)-2-acetoxy-3-tert.-butylamino-propane [obtainable from Na o-(2-methoxyethoxymethyl)-phenolate and 1-bromo-2-acetoxy-3-tert.-butylaminopropane] were boiled for 2 hours with 250 ml. of 10% ethanolic NaOH. The mixture was evaporated and worked up in the customary manner to give 1-(o-2-methoxyethoxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol, fumarate, m.p. 115°.

The examples which follow relate to pharmaceutical formulations which contain amines of formula I or their acid addition salts:

EXAMPLE A: TABLETS

A mixture of 1 kg. of 1-(p-allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol hydrochloride, 4 kg. of lactose, 1.2 kg. of potato starch, 0.2 kg. of talc and 0.1 kg. of magnesium stearate was pressed into tablets using conventional procedures in such a way that each tablet contained 10 mg. of active compound.

EXAMPLE B: DRAGEES

Tablets were pressed as in Example A and then conventionally coated with sucrose, potato starch, talc, tragacanth and a dyestuff.

EXAMPLE C: CAPSULES

2 kg. of 1-(o-2-Methoxyethoxymethyl-phenoxy)-3-tert.-butylamino-propan-2-ol fumarate were conventionally filled into hard gelatine capsules, so that each capsule contained 20 mg. of the active compound.

EXAMPLE D: AMPOULES

A solution of 1 kg. of 1-(o-allyloxymethyl-phenoxy)-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol fumarate in 30 l. of doubly distilled water was filtered sterile, filled into ampoules and lyophilized and sealed under sterile conditions. Each ampoule contained 1 mg. of active compound.

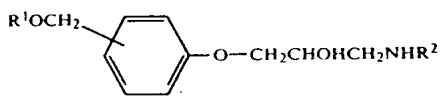
Tablets, dragees, capsules and ampoules which contain one or more of the remaining active compounds of the formula I and/or their physiologically acceptable acid addition salts can be obtained analogously.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. Phenoxy-amino-propanols of the formula



wherein R^1 is p-alkoxyalkyl with 2–6 C atoms; and R^2 is alkyl or hydroxyalkyl with 1–6 C atoms in each case, cycloalkyl with 3–8 C atoms or aralkyl or aralkyl wherein the aryl radical is mono- to tri-substituted by alkyl, alkoxy, OH, F, Cl or combinations thereof, with a total of 7–15 C atoms in each case, and the physiologically acceptable acid addition salts thereof.

2. The phenoxy-amino-propanols of claim 1 wherein R^1 is, 2-alkoxyethyl with 3–5 C atoms.

3. The phenoxy-amino-propanols of claim 1 wherein R^2 is alkyl of 1–6 C atoms.

4. The phenoxy-amino-propanols of claim 1 wherein R^2 is tert.-butyl.

5. The phenoxy-amino-propanols of claim 1 wherein R^2 is isopropyl, tert.-butyl, 2-phenylethyl, 1,1-dimethyl-2-phenylethyl or 2-(3,4-dimethoxyphenyl)-ethyl.

6. The phenoxy-amino-propanols of claim 1 wherein R^2 is alkyl with 1–6 C atoms, phenylalkyl with 7–10 C atoms or phenylalkyl wherein phenyl is mono- to tri-substituted by methoxy, with a total of 9–13 C atoms.

7. A pharmaceutical composition which comprises an amount of a compound of claim 1 effective for achieving isoprenaline-antagonism on the heart rate or blood pressure, and a pharmaceutically acceptable adjuvant.

8. A method of achieving isoprenaline antagonism on the heart rate or blood pressure in a mammal, which comprises administering to a mammal an amount of a compound of claim 1 which is effective for achieving isoprenaline-antagonism on the heart rate or blood pressure.

9. 1-(p-2-Isopropoxyethoxymethyl-phenoxy)-3-isopropylamino-propan-2-ol, a compound of claim 1.

* * * * *

Attachment A

IND Activities Date

Filing dates of INDs:

Date of submission to FDA: August 17, 1984 IND 24 773 (Hypertension)
Date of receipt at FDA: August 20, 1984

Date of submission to FDA: March 15, 1985 IND 26 072 (Angina)
Date of receipt at FDA: March 25, 1985

September 27, 1984	Quincy* to FDA	Amendment 1 / Hypertension
September 28, 1984	Quincy to FDA	Amendment 2 / Hypertension
October 08, 1984	Quincy to FDA	Amendment 3 / Hypertension
October 31, 1984	Quincy to FDA	Amendment 4 / Hypertension
December 04, 1984	Quincy to FDA	Asking for a meeting
January 02, 1985	Quincy to FDA	Amendment 6 / Hypertension
January 15, 1985	Quincy to FDA	Amendment 7/ Hypertension
January 31, 1985	Quincy to FDA	Amendment 8 / Hypertension
March 08, 1985	Quincy to FDA	Amendment 9 / Hypertension
May 24, 1985	EMD to FDA	Permission of state of Hesse, (Germany) to export trial medication.
June 05, 1985	Almedica, Waldwick, N.J. to FDA	Amendment 10 / Hypertension
July 31, 1985	Quincy to FDA	Amendment 11 / Hypertension
August 12, 1985	Quincy to FDA	Amendment 1 / Angina
August 13, 1985	Quincy to FDA	Amendment 2 / Angina
September 09, 1985	Quincy to FDA	Amendment 3 / Angina
September 09, 1985	Quincy to FDA	Amendment 12 / Hypertension
September, 1985	Quincy to FDA	Amendment 13 / Hypertension
September 29, 1985	Quincy to FDA	Amendment 4 / Angina
October 09, 1985	FDA to Quincy	FDA review comments
December 21, 1985	Quincy to FDA	Amendment 5 / Angina
December 26, 1985	Quincy to FDA	Amendment 6 / Angina
January 07, 1986	Quincy to FDA	Amendment 7 / Angina
January 26, 1986	Quincy to FDA	Transfer of Sponsorship
February 26, 1986	FDA to Quincy	Change of Sponsor (Lederle)

- Quincy Research Management Services
  Kansas City/Missouri
  acting as CRO for EMD

Lederle assumed sponsorship of E. Merck's IND	4/10/86
End of Phase II meeting	6/19/86
Amendment	9/24/86
Protocol Amend. New Protocol 57-20	1/6/87
Protocol Amend. New Protocol 57-17	10/8/87
Pre-NDA meeting	6/23/88
Protocol Amend. New Protocol 57-24	11/1/88
Protocol Amend. New Protocol 57-25	11/18/88
Protocol Amend. New Protocol 57-30	2/14/89
Protocol Amend. New Protocol 57-29	10/31/89
Inform. Amend. Pharm./Tox	8/23/89
Chemistry: (Questions to Quincy Research	3/30/89
Representing E. Merck, 10/9/85)	In NDA
Meeting with Dr. Temple	4/4/89
Protocol Amend. New Protocol 57-33	9/25/90
Protocol Amend. New Protocol 57-34	10/30/90
Information Amendment	2/4/91
Information Amendment Pharm/Tox	2/27/91

Attachment B

NDA Activities	Date
NDA filed	7/28/89
FDA Requests for Information re NDA W=Written T= Telephone	Lederle Response Written unless otherwise noted
10/13/89 W Summary Info on Pivotal Studies 57-1 and 57-3	10/20/89
10/19/89 W Chemistry: Specifications, Controls, Identity Tests, et al	12/27/89
10/30/89 T Chemistry: Samples/Dissolution Data	1/11/90 Telephone discussion 1/30/90 Samples sent
11/13/89 T Clinical: Info re Dropouts	11/22/89
12/5/89 T Clinical: Scatter Plots of lab data	2/13/90
1/3/90 T Clinical: Selected Case Records	1/11/90
3/16/90 T Clinical: Efficacy data from Hemodynamic study	3/16/90 Telephone discussion
4/16/90 T Pharmacology: Body wt. data, drug consumption in feeding studies	6/18/90 5/10/90 Meeting re Biopharm issues
5/30/90 T Clinical: More Info re Dropouts	6/18/90
6/7/90 T Chemistry: Packaging, scale-up, coatings	6/7/90 Telephone discussion
6/28/90 T Clinical: Efficacy data, E. Merck studies	8/9/90
7/18/90 Verbal request at FDA meeting: Pharmacology: Histopath tables	7/24/90 7/25/90 Telephone discussion 8/28/90 9/19/90
7/20/90 T Clinical: Treatment duration	9/10/90
7/23/90 T Chemistry: Manufacturing, packaging changes	7/23/90 Telephone discussion

NDA Activities	Date
FDA Requests for Information re NDA W=Written T= Telephone	Lederle Response Written unless otherwise noted
7/26/90 T Clinical:Add'l efficacy analyses	9/10/90
8/10/90 T Clinical:Clarification re dosing regimen; Response rates in open-label study	8/10/90 Telephone discussion
8/14/90 T Clinical: Dropout information	9/10/90
8/24/90 T Clinical: Clarification re "Other studies"	8/28/90 Telephone discussion 9/10/90
8/28/90 T Chemistry: Packaging	8/28/90 Telephone discussion
8/28/90 T Pharmacology: Summary tables	9/11/90 Telephone discussion
8/31/90 T Clinical: Peak/Trough assessments	9/7/90
9/21/90 T Clinical: Liver test data, Labeling	9/24/90 10/16/90 Telephone discussion 10/30/90
10/3/90 SBA meeting at FDA request: Request for E. Merck Drug Interaction Study	10/15/90
10/5/90 T Clinical: Pharmacokinetic data	10/12/90
10/16/90 T Clinical: Patient deaths	10/30/90
10/19/90 T Clinical: Clarification of efficacy data	10/30/90
11/8/90 T Clinical: Statistical questions	11/8/90 Telephone discussion
11/21/90 T Clinical: Patient deaths, patients with liver test abnormalities	11/26/90 12/3/90
12/12/90 W Chemistry: Product Monograph changes; coatings; electrodes	1/24/91
12/19/90 T Pharmacology: Definitions	1/7/91 Telephone discussion 1/11/91

NDA Activities	Date
FDA Requests for Information re NDA W=Written T= Telephone	Lederle Response Written unless otherwise noted
1/3/91 T Clinical: Statistical request	1/7/91
1/14/91 Pharmacology: Definitions; protocol clarifications	1/28/91
3/18/91 T Pharmacology Request to file repeat carci study to NDA	3/27/91
4/1/91 T Pharmacology: Request for data, tables, analyses, diskettes re to review of mouse carci study	5/1/91 5/13/91 Telephone discussion 5/22/91 5/30/91 6/11/91 8/7/91 8/8/91 Fax 8/9/91 Fax 8/9/91 (meeting) 8/29/91 (Telephone discussion) 10/22/91
7/2/91 T Clinical: Request for Liver test data	7/30/91 9/30/91 3/13/92

OTHER SUBMISSIONS

Safety Update	2/7/90
Summary Basis of Approval	1/18/91, 10/17/91
Revised Clinical Investigator's Brochure	2/4/91
Cardio-Renal Advisory Committee Information Package	4/8/91
Annual Report	6/10/87 7/28/88 9/18/89 11/16/90 12/4/91
Labeling	6/19/92 (Telephone discussion) 6/26/92 (Telepnone discussion) 7/6/92 Fax to FDA 7/8/92 Fax to FDA 7/9/92 (Telephone discussion) 7/20/92 Revised Package Insert submitted to FDA 7/23/92 Fax to FDA 7/24/92 Fax to FDA 7/28/92 (Telephone discussion) 7/30/92 Fax to FDA 7/30/92 Revised Package Insert submitted to FDA 7/30/92 Final Printed Labeling